



R E M A R K S

The applicants acknowledge the Examiner's comprehensive Office Action with appreciation. The Office acknowledges the telephonic election of restriction Group II and requests amendment to exclude any subject matter falling outside of the election. With this response, the applicants cancel Claims 27, 30 and 31 and any remaining subject matter falling outside the elected invention. Claims 18-26, 28-29 and 32-34 remain under consideration.

The Office requests that the applicants provide the structural make-up of substituent G in the Abstract of the Disclosure. Herewith please find a replacement Abstract which includes the requested information.

The Office raises several rejections for indefiniteness under 35 USC § 112, second paragraph. The applicants are asked to explain which "neutral seven membered" ring formed by substituents R_1 - R_4 may be aromatic. The applicants acknowledge the Office's concerns, but assert that neutral seven-membered rings do exist which exhibit aromatic character. These include tropone or tropolone, which rings are described in the text Advanced Organic Chemistry, Reaction, Mechanisms, & Structure, IV Ed., John Wiley & Sons, NY, p. 47 (1992), a extract of which is attached hereto. Thus, the applicants submit that the claim to aromatic 5-7-membered rings is definite according to those skilled in the chemical arts.

The Office also questions where the asymmetry exists in the compounds of Claims 29 and 32. In this regard, the applicants acknowledge the objection of the Office and remove the inappropriate isomer language from the claims.

Continuing within the indefiniteness rejection, the Office notes that the method claim to a particular mechanism of action is considered indefinite. The applicants note that the Method claim must recite the treatment of real world conditions for which there is support, either in the Specification, or implicitly as recognized by those skilled in the art. The applicants acknowledge the Office rejection and have, with this response, amended the Method claim to claim treatment of the real world conditions: "depression, anxiety, schizophrenia, Parkinson's disease, cognitive disorders, libido disorders and sexual dysfunction, sleep disorders, drug abuse, and impulsive behavior disorders." Support for the claim to treatment of these conditions may be found in the Specification in that the applicants disclose that $\alpha_2/5\text{-HT}_{2C}$ antagonists may be understood by those skilled in the art to be useful in treating such conditions (see page 2, lines 13-15, additional support for the treatment of such conditions being disclosed in the literature review at the top of the same page).

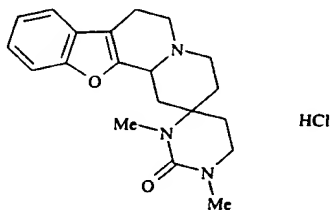
In an effort to provide the most comprehensive correlation between the compound activity demonstrated in the pharmacological examples and the amended claim to treatment of specific conditions, the applicants also provide a Declaration consisting of a literature review relevant to the instant inquiry. It is submitted that the applicants, with this Declaration, provide evidence that those skilled in the art would expect the $\alpha_2/5\text{-HT}_{2C}$ antagonist compounds of the instant invention to be effective in treating the disorders now claimed in the Method claim.

Under 35 USC § 112, first paragraph, the Office raises several rejections for lack of enablement. The claims are subject to rejection for failing to enable the broad scope of compounds claimed within the broad listing of substituents. With this response, the applicants amend the scope of the generic claim to claim

piperazine compounds. In addition, the applicants limit the T'₃ substituent to benzodioxinyl or optionally substituted benzodioxinylalkyl. It is submitted that the compounds exemplified in the Specification are now representative of the scope of compounds claimed.

The enablement rejection continues with a rejection for failing to demonstrate that the broad scope of compounds claimed possess the ability to treat any of the possible disease states disclosed within the Specification. The applicants submit that the Declaration supplied in response to the indefiniteness rejection in conjunction with the pharmacology provided in the Specification is responsive to the enablement rejection, as well, in that it is within the understanding of those skilled in the art that compounds possessing the instant compounds' $\alpha_2/5$ -HT_{2c} antagonist activity are expected to be effective in treating the conditions now claimed to be treatable.

The applicants also acknowledge the Office's exposition of the Brefel-Courbon, Hoffman and Katzung articles. In rebuttal, the applicants wish to point out that MERCK & CO. is presently in Phase I clinical trials with the α_2 antagonist MK-912 for treating depression. MK-912 is spiro{2H-benzofuro[2,3-a]quinolizine-2,4'(1'H)pyrimidin}-2'(3'H)-one, 1,3,4,5',6,6',7,12b-octahydro-1',3'-dimethyl, monohydrochloride, (2 S-trans).



Thus, the applicants submit that it is well established that α_2 antagonists are, indeed, being exploited for treating central nervous system conditions.

Finally, the compounds and methods claimed are rejected for lack of novelty under 35 USC § 102(b) based on the Duckworth, et al., U.S. Patent No. 5,905,080, disclosure. With this response, the applicants have amended the broad scope of the compounds claimed such that the rejection for anticipation and/or obviousness in view of Duckworth, et al. is now rendered moot. As Duckworth, et al. clearly notes, the preferred compounds are those in which R₄ is alkyl, "such as methyl". Consequently, the instant compounds wherein T'₃ is benzodioxinyl or optionally substituted benzodioxinylalkyl clearly do not read on the prior art disclosure.

In addition, the compounds and methods claimed are rejected for lack of novelty based on the disclosure of the Gaster, et al., U.S. Patent No. 6,159,979. The Office notes both compound examples and conditions treatable which are disclosed in the reference. As with the rejection over Duckworth, et al., the rejection, whether for anticipation or obviousness, over Gaster, et al. is now moot in view of the instant amendment.

* * * * *

Accordingly, entry of the present amendment and Declaration, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,
THE FIRM OF HUESCHEN AND SAGE

By:


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Enclosure: Postal Card Receipt,

Check No. 71345 for \$930 for three (3) month extension,

Claims amendment in Clean and Marked-up forms,

Replacement Abstract, and

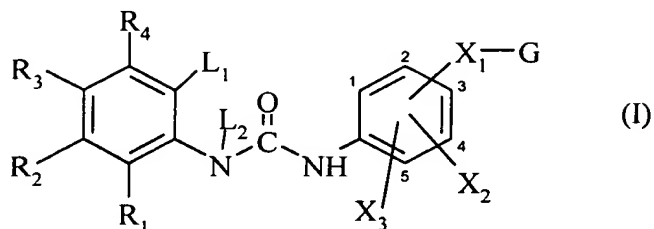
Declaration by Dr. MILLAN, accompanied by Form PTO-1449 listing the discussed references, as well as copies of each reference.

* * * * *

THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR DEFECT IN THE ATTACHED CHECK, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.

CLAIMS (Marked-Form)

18. A compound selected from those of formula (I) :

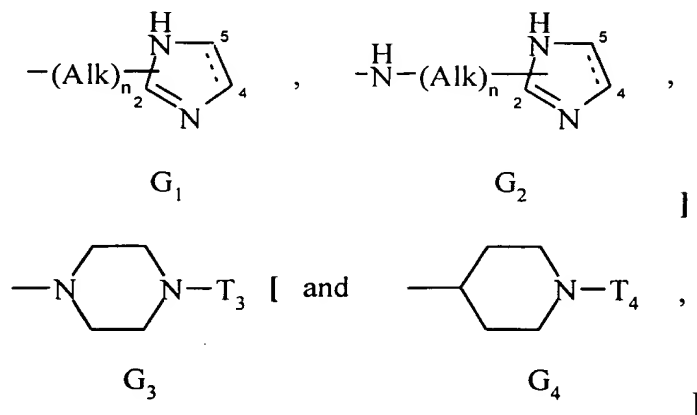


wherein

- ✓ R_1 , R_2 , R_3 and R_4 independently represent hydrogen, halogen or alkyl, alkoxy, hydroxy, alkylthio, mercapto, cyano, amino (optionally substituted by one or two alkyl), nitro, carboxy, alkoxycarbonyl, aminocarbonyl (optionally substituted by one or two alkyl) or carbamoyl,
or, taken in pairs, form together with the carbon atoms to which they are bonded a phenyl ring or an aromatic heterocycle having from 5 to 7 ring members and containing from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur,
- ✓ L_1 and L_2 each represents hydrogen or together form $-\text{CH}_2-\text{CH}_2-$,
- ✓ X_1 , attached at the 2 or 3 position of the aromatic ring, represents a bond, and in that case X_2 represents hydrogen, halogen, alkyl, alkoxy, hydroxy, nitro or cyano, or amino (optionally substituted by one or two alkyl),
or,
 X_1 and X_2 , together with two adjacent carbon to which they are bonded in the 2, 3 or 4 position of the aromatic ring, form (C_4-C_7) cycloalkyl wherein one or two $-\text{CH}_2-$ of the cycloalkyl ring are optionally replaced by oxygen or NH (optionally substituted by alkyl) and wherein one carbon of the cycloalkyl ring is substituted by G,

- ✓ X_3 represents hydrogen, halogen, alkyl, alkoxy, hydroxy, nitro or cyano, or amino (optionally substituted by one or two alkyl),

- ✓ G represents [a group selected from :



wherein :

- ✓ the broken lines indicate the optional presence of a double bond,
- ✓ Alk represents linear or branched (C_1 - C_6)alkylene wherein, when G_1 or G_2 contains imidazoline, the group Alk- is attached at the 2 position of the ring,
- ✓ n is 0 or 1,
- ✓ T_3 represents [alkyl, optionally substituted aryl, optionally substituted arylalkyl,] optionally substituted heteroaryl or optionally substituted heteroarylalkyl, [
- ✓ T_4 represents alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl,]

wherein :

- the term "alkyl" denotes linear or branched group containing from 1 to 6 carbon,
- the term "alkoxy" denotes linear or branched alkyl-oxy containing from 1 to 6 carbon,

- the term "aryl" denotes phenyl, naphthyl or biphenyl,
- the term "heteroaryl" denotes a benzodioxinyl group [an aromatic monocyclic group, or a bicyclic group in which at least one of the rings is aromatic, each group containing from 5 to 11 ring members and from 1 to 5 hetero atoms selected from nitrogen, oxygen and sulphur],
- the expression "optionally substituted" associated with aryl, arylalkyl, heteroaryl and heteroarylalkyl denotes that those groups are unsubstituted or substituted on the cyclic moiety by one or more halogen and/or alkyl, alkoxy, hydroxy, mercapto, alkylthio, cyano, amino (optionally substituted by one or two alkyl), nitro, carboxy, alkoxycarbonyl, aminocarbonyl (optionally substituted by one or two alkyl) or carbamoyl, wherein heteroaryl and heteroarylalkyl may in addition be substituted by oxo, its

enantiomers and diastereoisomers thereof, and addition salts thereof with a pharmaceutically acceptable acid or base.

20. A compound of claim 18, wherein L_1 and L_2 together form $-CH_2-CH_2-$.

26. Compounds of claim 18, wherein R_3 and R_4 together with carbon to which they are bonded form a phenyl ring and L_1 and L_2 together form $-CH[1]_2-CH_2-$.

29. A compound of claim 18 that is *N*-(3-chloro-4-methylphenyl)-*N'*-(3-[4-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-piperazinyl]phenyl)urea, its [enantiomers and diastereoisomers thereof, and] addition salts thereof with a pharmaceutically acceptable acid or base.

32. Compound of claim 18 that is *N*-(3-[4-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-piperazinyl]phenyl)-*N'*-(3,4-dimethylphenyl)urea, its [enantiomers and diastereoisomers thereof, and] addition salts thereof with a pharmaceutically acceptable acid or base.

33. A method for treating an animal of human living body afflicted with [a condition which is treatable with a dual $\alpha_2/5$ -HT_{2c} antagonist] depression, anxiety, schizophrenia, Parkinson's disease, cognitive disorders, libido disorders and sexual dysfunction, sleep disorders, drug abuse, and impulsive behaviour disorders comprising the step of administering to the living body an amount of a compound of claim 18 which is effective for alleviation of said condition.

34. A pharmaceutical composition useful for treating an animal of human living body afflicted with a condition selected from depression, anxiety, schizophrenia, Parkinson's disease, cognitive disorders, libido disorders and sexual dysfunction, sleep disorders, drug abuse, and impulsive behaviour disorders [which is treatable with a dual $\alpha_2/5$ -HT_{2c} antagonist] comprising a compound of claim 18 in combination with one or more pharmaceutically acceptable, excipients or vehicles.